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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
SZPERKA, MICHAEL EDWARD

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,569	SAINT-REMY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,13-20 and 22-33* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received July 10, 2006 are acknowledged.

Claims 1, 5-12, and 21 have been canceled.

Claim 33 has been added.

Claims 2-4, 13-20, and 22-33 are pending.

Claims 2-4 and 13-20 stand withdrawn from consideration as being drawn to nonelected inventions. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the Office Action mailed January 2, 2004.

Claims 22-33 are under examination as they read on methods of treating SIRS by administering an antibody, wherein the antibody is a partial inhibitor of blood coagulation factor VIII

Applicant's amendment to the first line of the specification to update priority information is acknowledged. However, this amendment does not indicate the relationship of application 10/030,522 to the instant application. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

3. Claims 22-32 stand rejected and new claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The prior office action mailed January 1, 2006 states that:

The claimed invention recites a method for the prevention or treatment of SIRS using an antibody that binds FVIII, and the specification discloses in lines 35-36 of page 1 that sepsis is a species of SIRS. Clinical signs and symptoms used to diagnose SIRS include presentation with two or more of the following: hyper- or hypothermia, tachycardia, tachypnea, and leukocytopenia (the Merck Manual of Diagnosis and Therapy, seventeenth edition, 1999, pages 1143-1147, particularly the top of the right column of page 1144). Applicant's claimed method appears to work because the administered monoclonal antibody interferes with the ability of FVIII to participate in the coagulation cascade, thus preventing systemic problems with excessive coagulation that often develop in patients suffering from SIRS/sepsis. It should be noted that excessive coagulation is not regarded as a sign or symptom for diagnosis of SIRS/sepsis, and that sepsis can occur in patients with impaired coagulation, such as hemophilia A patients (Ferenz et al., Clin. Orthop. Relat. Res., 1989, 244:254-257, see entire document, particularly the abstract and Cobb, J. Rheumatol., 1984, 1:87-89, see entire document, particularly the abstract). As such, administering an inhibitory anti-FVIII antibody would not be effective in all patients suffering from sepsis since not all sepsis patients exhibit excessive coagulation. Further, the instant methods are recited as preventing as wells as treating SIRS. As discussed above, prevention of SIRS with anti-FVIII antibodies presumably occurs by preventing FVIII from joining the tenase complex and thus limiting thrombin generation *in vivo* (see also lines 25-37 of page 4 of the specification). It is known that thrombin can be generated by many pathways, some of which do not require FVIII (Price et al., Anaesthesia, 2004,59:483-492, see entire document, particularly Figures 1 and 2). As such, coagulation can occur even in the presence of FVIII inhibitors (see also lines 31 and 32 of page 4 of the specification), and therefore SIRS/sepsis can also occur in the presence of FVIII inhibitors. Also, in order to prevent SIRS/sepsis, therapy would need to begin before the condition was diagnosed and the disclosure does not appear to teach how to select patients that will or will not develop SIRS/sepsis before the signs and symptoms of these conditions are clinically apparent. Additionally, since applicant's method works by inhibiting FVIII function, and hemophilia A patients are characterized by inhibited and/or absent FVIII activity, it appears that it would be impossible to use applicant's method to treat or prevent SIRS/sepsis in hemophilia A patients. In light of the above, it appears that it may be possible to treat patients that have SIRS/sepsis and exhibit excessive coagulation using anti-FVIII antibodies, but it does not appear reasonable that SIRS/sepsis can be prevented or that it can even be treated in all patients diagnosed with SIRS/sepsis.

Applicant has argued that the disclosed experimentally induced mouse sepsis model is sufficient to enable the full breath of the claimed method. Prior office actions had discussed the teachings of Freeman et al. and Taylor et al. (both of record) to demonstrate that sepsis is a complicated condition that involves multiple physiological pathways and that promising results from animal models of sepsis are not routinely confirmed when such methods are used to treat human patients with sepsis. Applicant argues the specifics of the teachings of Freeman et al. and Taylor et al. and attempts to characterize the references as irrelevant since they do not teach the exact methodology being claimed. The examiner agrees that neither Freeman et al. nor Taylor et al. teach the instant method, but this does not mean that the general teaching of unpredictability concerning the extrapolation of promising model system data to the treatment of humans. Indeed, Riedemann et al. state "The history of sepsis trials has suggested that experimental models of sepsis differ significantly from human sepsis, and that infusion of endotoxin (LPS, the model system used by applicant) does not appear to accurately reflect the mechanisms responsible for sepsis in humans" and "Many of the human clinical trials (for treating sepsis) were based upon findings in rodents and, to an extent, in subhuman primates, with the assumption that these can be extrapolated to human sepsis. Such extrapolation may not be valid." (Expert Opin. Biol. Ther. 2003, 3:339-350, see entire document, particularly the first full paragraph of the left column of page 346 and the first paragraph of the conclusions section). As such it appears reasonable that applicant's claimed method would not be expected to work in humans even with applicant's declaration received October 20, 2005 demonstrating the ability to treat and prevent LPS-induced sepsis in mice by administration of the KRIX1 antibody. Applicant argues that animal models are routinely used in biomedical research, and cites references wherein antibodies that bind molecules other than FVIII were administered to treat sepsis in animal models. The examiner agrees that the use of animal models is routine, but based upon the combined teachings of Freeman et al., Taylor et al., and Riedemann et al. it does not appear that animal model systems of sepsis have predictive value in determining clinical effectiveness in human sepsis.

Applicant also argues that the instant specification is enabled for the entire genus of anti-FVIII antibodies recited in the instant method claims, including those with 80% or > identity to the CDRs of KRIX1, because screening hybridomas for the requisite functional activity is not undue, and antibodies with CDRs with 80% or > identity could be made using KRIX1 as a starting material in know methodologies such as alanine scanning, site directed mutagenesis, and codon-based mutagenesis. The examiner disagrees with applicant's arguments that no more than routine experimentation is required, and maintains that generation of the entire genus of recited antibodies is unpredictable.

Antibody binding to antigen is primarily due to interactions between the CDRs of the antibody and the epitope of the antigen that is being recognized, with all 6 antibody CDRs (3 on the heavy chain and 3 on the light chain) being important for this process (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection). The antibodies used in the instant methods are disclosed as being partial inhibitors of FVIII, with the specification defining the percent inactivation of FVIII caused by the inhibitor as ranging from 25-99% and providing a method to test for activity (see particularly lines 1-14 of page 11). The precise epitope bound by KRIX1, or by the genus of recited antibodies, that allows for the partial inhibition of FVIII activity is not known other than that it is in the C1 domain of FVIII.

Rudikoff et al. (of record) disclose that even a single point mutation in an antibody CDR can eliminate antigen binding. The immunological phenomenon of somatic hypermuation preferentially introduces point mutations into the variable domains of antibodies, the majority of which have a negative impact on antigen binding thus leading to apoptosis of the cells possessing such mutations (Janeway et al., Immunobiology, sixth edition, 2005, pages 379-381 see entire selection). Given that it is recognized in the art that most changes to the antigen binding domains of antibodies are deleterious, it does not appear that one can predict sequences that will bind antigen or predict how such sequences can be modified without altering antigen binding. The specification does not appear to discuss which residues in the CDRs of KRIX1 can be mutated and yet retain the functional activity of KRIX1, and the art cited by applicant for how to make antibodies of at least 80% CDR identity appears to rely on the generation of essentially random mutations in an antibody sequence followed by selection without any apparent knowledge of what the ultimately selected sequence will look like. Given the fact that most mutations to antigen binding domains are deleterious, the fact that the identity of mutations that are not deleterious cannot be predicted *a priori*, and the incomplete characterization of the antigen bound by the antibodies recited in the instant methods, it does appear that identification of the genus of antibodies recited in the instant methods is unpredictable. Further, it is not clear if each CDR must be 80% identical to a CDR in KRIX1, or if the 80% identity limitation need only apply to one CDR of each chain, thus allowing the other 4 CDRs to be more divergent in sequence. If applicant does intend for all 6 CDRs to be 80% identical to the 6 CDRs of KRIX1, the claim language does not clearly specify that, for example, CDR1 of the heavy chain is 80% identical to CDR1 of the heavy chain of KRIX1. This is important because a large percentage of antibody-antigen interactions occur in CDR3, and therefore an antibody containing a heavy chain CDR3 sequence that is 80% identical to the heavy chain CDR1 of KRIX1 would not be expected to maintain the binding properties of KRIX1.

Additionally, it is known that anti-FVIII antibodies can be isolated from healthy individuals, some of which inhibit FVIII activity (Gilles et al., J. Clin. Invest. 1994, 94:1496-1505, see entire document particularly the abstract). These inhibitory antibodies generally do not cause clinically evident problems due to the presence of anti-idiotypic antibodies that inhibit the binding of anti-FVIII antibodies to FVIII. As such, administration of KRIX1 or any other anti-FVIII antibody may not be effective due to the presence of preformed anti-idiotypic antibodies present in the patient's circulation.

Therefore, based upon the fact that applicant's method appears to work by inhibiting coagulation, the fact that SIRS/sepsis can be present in an individual in the absence of coagulation or functional FVIII, the fact that coagulation can occur through multiple pathways many of which do not require FVIII, the fact that animal model data concerning sepsis is not predictive of human sepsis, the fact that generation of antibodies other than KRIX1 that have the properties required for performing the instant method is not predictable, and the fact that many individuals have preformed anti-idiotypic antibodies that can potentially neutralize the anti-FVIII antibodies administered by the instant method, a skilled artisan would be unable to practice the full scope of applicant's claimed method without performing additional research.

Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive. Applicant first repeats arguments of record that undue experimentation is not required to make the genus of antibodies recited for use in the instant methods in light of the disclosed working examples.

Undue experimentation is required to make the genus of antibodies recited in the instant method claims for the reasons of record provided supra. Further, the working example is limited to a single antibody, KRIX 1, and applicant has not disclosed which

amino acids of KRIX 1 can or cannot be changed commensurate with retention of the functional activities of KRIX 1, and in view of the fact that even single amino acid changes in an antibody can disrupt antigen binding, undue experimentation is required since the disclosed screening methods do not provide guidance and instead rely upon repeated trial and error.

Applicant's second argument is that the specification supports methods of prevention as well as treatment due to the disclosure of the administration of KRIX 1 to mice previously injected with LPS.

These arguments are not convincing because prevention requires the recited method to be completely effective in all patients at all times. Applicant has provided a mouse model based upon administration of LPS, but as discussed previously on the record, model systems in this area do not appear to be fully representative of reactions occurring in the genus of all mammals. In applicant's model system, the administration of KRIX 1 reduced, but did not prevent, fibrin deposition in normal mice while mice genetically deficient for FVIII demonstrated no reduction in fibrin deposition. Note that fibrin deposition is one of the many signs and symptoms of SIRS.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

As discussed in the rejection of record, it does not appear that administration of applicant's genus of antibodies would work 100% of the time in 100% of patients. This

is especially true given the multiple pathways by which the signs and symptoms of SIRS arise and because some patients comprise factor VIII activity that is already inhibited due to mutations or preexisting inhibitory antibodies as discussed in the rejection of record. Further, applicant's disclosed data from the murine LPS system appear to support treatment in that fibrin deposition is reduced, but not prevention in that fibrin deposition was observed even in the presence of KRIX 1. Therefore, it is reasonable that a skilled artisan would not accept without question that applicant's claimed method would work as recited, and as such undue experimentation is required before a skilled artisan can practice the full scope of applicant's recited methods.

4. Claims 22-32 stand and new claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the reasons of record. The office action mailed December 15, 2004 states that:

> Applicant is not in possession of a method for preventing and/or treating Systemic Inflammatory Response Syndrome in a mammal by administering a partial inhibitor of factor VIII to the said mammal which is a monoclonal antibody against Factor VIII or an antigen binding fragment of said monoclonal antibody, said antibody or fragment being able to recognize epitopes located in the C1 domain of Factor VIII in claim 22, wherein monoclonal antibody or fragment of said antibody comprises a variable heavy sequence being at lest 80% identical to the amino acid sequence depicted I figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9 in claim 31.
>
> Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (of antibody comprises a variable heavy sequence being at least 80% identical VH and/or VL) to describe the claimed genus, nor does it provide a description of structural features that are common to species. As discussed above, the specification provides no structural description of such antibodies other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed the monoclonal antibody sequences looks like.

And the office action mailed January 9, 2006 states that:

> Applicant's arguments filed October 20, 2005 have been fully considered but they are not persuasive. Applicant argues that the specification does provide adequate written description of the invention, that skilled artisans are well aware of the general structure of antibodies, and that the sequence of the human monoclonal antibody KRIX 1 is sufficient to support the genus of antibodies containing 80% or greater identical CDR sequences that binds the C1 domain of FVIII. The examiner agrees that the general structure of antibody molecules is well known, but the examiner disagrees that disclosure of the sequence of KRIX1 is sufficient to support the claimed genus of antibodies.

Applicant has recited that the claimed antibodies must recognize epitopes (i.e. bind to epitopes) located in the C1 domain of FVIII. The specification discloses that the epitope bound by KRIX1 is conformational, but the precise structure of this conformational epitope is not disclosed. It is known in the art that antibodies that bind FVIII but that do not inhibit the ability of FVIII to partake in coagulation can be isolated from hemophilia patients as well as normal individuals (Gilles et al., Blood, 1993, 82:2452-2461, Gilles et al., J Clin Invest, 1994, 94:1496-1505, and Scandella et al., Blood, 1989, 74:1618-1626, see the entirety of all documents, particularly their titles and abstracts). Indeed, Gilles et al. conclude that a majority of the determinants recognized by antibodies that bind FVIII are nonfunctional (Gilles 1993, see particularly the first full paragraph of the left column of page 2460). As such, it does not appear reasonable that any generic antibody that binds the C1 domain of FVIII would have the requisite properties that allow for its use in the instant claimed method, and it also does not appear reasonable that applicant has possession of other antibodies that bind the same epitope of FVIII as KRIX 1 since the epitope bound by KRIX 1 does not appear to be sufficiently known or described.

Applicant's argument that the disclosure of the sequence of KRIX 1 provides adequate description of the claimed genus is also not convincing. As taught by Janeway et al., the CDR regions are primarily responsible for antigen binding, with all 6 CDR sequences (3 on the antibody heavy chain and 3 on the antibody light chain) being involved in the interaction (Immunobiology, third edition, 1997, pages 3:7-3:11, see particularly the top of page 3:8). Claim 31 requires the claimed antibodies to have at lest 80% identity in the CDRs, while other claims are broader in that they presumably can have any sequence. Any sequence with less that 100% identity will have at least one mutated amino acid residue. In the body, the natural process of somatic hypermutation preferentially introduces point mutations into the antigen binding domains of antibodies, with most of the mutations resulting in a negative impact on antigen binding (Janeway et al. Immunobiology, sixth edition, 2005, pages 379-381, see entire selection). Such deleterious mutations are frequent events that are disastrous for the B cells that harbor such mutations since B cells with decreased antigen binding potential die by apoptosis (Janeway et al., 2005, see particularly the first full paragraph of page 380). The potential deleterious nature of point mutations in CDRs is also taught by Rudikoff et al. (of record) wherein a single amino acid change completely abrogated antigen binding. The specification does not appear to provide any guidance as to which specific residues in the CDR regions of KRIX 1 can be mutated without disrupting binding to the C1 domain of FVIII, nor does it appear to provide a description of the sequence of other antibodies that bind the C1 domain that are not constrained by the percent identity limitation. As such, given the apparent lack of specificity concerning the structure of the epitope that is bound by the claimed antibodies and the art recognized problem that most changes to the antigen binding sequences are deleterious and that even single point mutations can completely eliminate binding, a skilled artisan would reasonably conclude that while applicant was in possession of the KRIX1 antibody, applicant did not possess the claimed genus of anti-FVIII antibodies.

Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive. Applicant argues that they did possess the recited genus of antibodies as evidenced by the disclosure of two antibodies that bind the C1 domain and partially inhibit FVIII activity.

This argument is not convincing for the reasons of record. Further, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins). Applicant argues that the specification discloses two members of the recited genus of antibodies. Upon review, the specification appears to disclose three antibodies, KRIX 1, BO2C11, and MoAb4H1D7. KRIX 1 is disclosed as comprising the functional properties of binding the C1 domain and partially inhibiting the activity of FVIII. BO2C11 binds the

C2 domain of FVIII as evidenced by Jacquemin et al. and as such is not a member of the recited genus (of record as reference 6 on the 4/16/02 IDS, see particularly the abstract). MoAb4H1D7 is disclosed as binding the complex of FVIII and von Willebrand factor (vWF, see Example 4) and since the specification teaches that vWF binds FVIII using the C2 and A3 domains (see particularly lines 20-25 of page 8), it does not appear that MoAb4H1D7 is a member of the recited genus. As such, it appears that the specification discloses only one member of the genus of antibodies recited in the independent claim. As previously discussed, the specification does not disclose the precise epitope recognized by the recited genus of antibodies, nor does it identify the structure an antibody must comprise in order to comprise the recited function.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3). As discussed above, the specification does not appear to disclose a representative number of species, nor does it appear to disclose a structure that is correlated with the recited functional properties. Therefore, a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of antibodies at the time the application was filed, and as such the recited genus does not have adequate written description in the specification as filed.

5. No claims are allowable.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
September 6, 2006

9/14/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER